57. The formulation of claim 9 wherein the bioactive peptide is selected from the group consisting of toxins affecting the presynaptic neurojunction, toxins affecting the postsynaptic neurojunction, toxins affecting ion channels, and toxins that damage the cell membrane.

63. The formulation of claim 62 wherein the bioactive peptide is a protein hormone selected from the group consisting of oxytocin, arginine vasopressin, insulin, growth hormone and calcitonin.

Remarks

Claims 1 and 3-69 are pending, and claims 37, 43, 57, 63 have been editorially amended in the manner suggested by the Examiner.

The objection to claims 37, 43, 57 and 63 has been rendered moot in view of the above amendment of these claims.

The rejections under Section 103(a) are respectfully traversed. Mundshenk '407 is cited for its teaching of the preparation of inactivated bioactive peptides, while Heiber et al. is cited for "buccally administered peptides", and Cardinaux et al. for mucosal peptide formulations with benzalkonium chloride as preservative.

The Action combines these three disparate references, and asserts that they render the invention obvious. As described previously, however, none of the references, either alone or in suitable combination, teach or suggest the use of the quaternary ammonium salt (such as benzalkonium chloride) to *enhance* the permeation of a inactivated bioactive peptide into the *mucosal* surface. Of these references, only Cardinaux even mentions the use of benzalkonium chloride, though it does so only within a "laundry list" of other suitable compounds, and then only for its conventional use as a preservative.

Applicants appreciate, but respectfully disagree, with the Examiner's positions regarding hindsight reasoning and the propriety of combining these references. Putting aside these issues, however, it remains clear that the Action relies in large part, if not entirely, on the single, unsupported assertion that "[i]nclusion of benzalkonium chloride in such a combined formulation *would inherently* provide the enhanced mucosal absorption of the peptide in the buccal cavity" (emphasis added). This assertion simply fails to rise to the level necessary to establish a *prima facie* showing under Section 103. Clearly nothing in the references teaches or suggests such a method or system. To the contrary, the cited references themselves either describe the inclusion of benzalkonium chloride for its conventional use as a preservative, or at levels far different (and likely far more disruptive to the tissue) than those presently claimed. Nor does this assertion even begin to address the many, and varied, limitations set forth in Applicants' pending dependent claims, the patentability of which is apparent for the reasons provided above and for others as well.

Although the references of Acharya, Costa et al. and Fang et al. are *mentioned* thereafter, they are neither relied upon in the statement of the rejection, nor do they support this assertion.

Acharya ('094) describes an entirely unrelated polymeric delivery system and includes a single, passing mention of the optional use of adjuvants "such as benzalkonium chloride that also assist medicinal agents in passing through the mucosa and into the blood stream."

Costa et al. describes a *transdermal* (as opposed to buccal) delivery system for lorazepam (as opposed to peptides), and includes benzalkonium chloride at levels (1% and 5%) that tend to be far in *excess* of Applicant's preferred concentration ranges (see, e.g., claims 13 and 14). If anything, the reference would seem to teach away from the present invention, since it also refers to the manner in which cationic enhancers (such as benzalkonium chloride) tend to provide increased flux, but are *"more damaging"* than anionic or nonionic surfactants.

Finally, Fang et al. was cited and distinguished previously by Applicants, as teaching merely the *combination* of benzalkonium chloride and a cationic surfactant to provide an enhancing effect in the iontophoresis of enoxacin.

With regard to the second Section 103(a) rejection, Kamiya et al. is merely included as teaching the use of spraying to administer peptides. Putting aside its own deficiencies, this reference adds nothing to remedy the various shortcomings described above with respect to the combination of Mundshenk and Cardinaux et al.

Accordingly, reconsideration of the pending rejection and allowance of the claims as amended above is respectfully requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments to the claims (where insertions are underlined and deletions placed in brackets):

37. The system of claim[s] 7 wherein the bioactive peptide is selected from the group consisting of toxins affecting the presynaptic neurojunction, toxins affecting the postsynaptic neurojunction, toxins affecting ion channels, and toxins that damage the cell membrane.

43. The system of claim[s] 37 wherein the bioactive peptide is a protein hormone selected from the group consisting of oxytocin, arginine vasopressin, insulin, growth hormone and calcitonin.

57. The formulation of claim[s] 9 wherein the bioactive peptide is selected from the group consisting of toxins affecting the presynaptic neurojunction, toxins affecting the postsynaptic neurojunction, toxins affecting ion channels, and toxins that damage the cell membrane.

63. The formulation of claim[s] 62 wherein the bioactive peptide is a protein hormone selected from the group consisting of oxytocin, arginine vasopressin, insulin, growth hormone and calcitonin.